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ORGANIC REACTIONS IN THE AQUEOUS MEDIUM (1,2)
Part-III. Reactions of Hexamethylenetetramine with Active Methylene Compounds

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Reactions of hexamethylene tetramine with active methylene compounds like ethyl acetoacetate, acetylacetone, dimedone and dibenzoylmethane have been thoroughly investigated. These investigations have led to the successful development of simple, convenient and economical methods for the synthesis of pure diethyl 1,4-dihydro-2, 6-dimethyl-3, 5-pyridinedicarboxylate (I) and 3,5-diacetyl-1,4-dihydro-2,6-dimethylpyridine (II) in 74.5 and 53.1% yields respectively, under mild aqueous conditions. The yields of these dihydropyridines have been related to the extent of keto forms of ethyl acetoacetate and acetylacetone in the aqueous medium, where intramolecular hydrogen-bonding cannot operate. Conditions have also been developed for the synthesis of dihydropyridine derivative of dimedone, along with its methylene-*bis*-compound and its formation rationalised through its enol-chelate stabilization. The failure of dibenzoylmethane to go beyond its methylene-*bis*-compound has been interpreted in terms of its preferred *anti*-configuration. The structure of the compounds synthesised have been elucidated using i.r. n.m.r. and mass spectra.

Key words: Active methylene compounds, Dihydropyridine derivatives, Methylene-*bis*- (β-diketones).

Introduction

Hexamethylenetetramine (hexamine) finds diversified uses [3-27]. In addition, certain dihydropyridines have been synthesised by the reaction of hexamine and ethyl thioacetoacetate in the presence of ammonium acetate [28]. The synthesis of menthyl esters of 2,6-dimethyl-1,4-dihydro-3, 5-dicarboxylic acids has been reported [29]. The preparation of pyridines by cyclo-condensation of aldehydes or ketones and ammonia in the liquid phase using continuous injection of carbonyl compounds has also been reported [30]. In literature one finds that Hantzch synthesis is the most widely used general procedure for the synthesis of pyridine derivatives using Knoevenagel and Michael condensations followed by cyclisation reactions [31-35].

Hexamine has been used as an aminomethylating agent in the preparation of certain derivatives of 1,3-diazadmantane 6-ones [36-38] in the non-aqueous medium. However, reactions of hexamine with active methylene compounds to form dihydropyridines have rarely been investigated, especially in the aqueous medium. Moreover, the methods presently employed for the preparation of dihydropyridines involve different stages, are lengthy and quite tedious [39-42]. Consequently, the reaction of hexamine with ethyl acetoacetate, acetylacetone, dimedone and dibenzoyl-methane have been investigated in an attempt to obtain dihydropyridine derivatives of these compounds in the aqueous medium. Thus, we have been successful in developing very convenient, simple, economical and single step procedures for the formation of dihydropyridine derivatives especially those of ethyl acetoacetate and acetylacetone which are very costly (43). Dihydropyridine derivative of dimedone, methylene-*bis*-(β-diketones) of dimedone and dibenzoylmethane have also been obtained.

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Experimental

General. The solvents and chemicals used were either of analytical grade or were purified by distillation just before use. Distilled water was used in all the experiments and pH's were recorded by noting the natural pH of the reaction mixture as soon as it became homogeneous or soon after the addition of acid or alkali. Experiments at room temperature (30±3°) and below room temperature (13±2°) were performed in stoppered flasks. Experiments in non-aqueous and aqueous-solvent mixtures were carried out in glass apparatus fitted with reflux condenser at 72±3° and also under mild reflux. The products formed were isolated by filtration at water-jet pump, and after washing several times with small lots of water, were dried first in an oven at 100°-105° for 3-4 hr and then at room temperature in a vacuum disiccator for 2-3 days. These were purified 2-3 times by recrystallization from appropriate solvents and identified by determining their mixed melting points with authentic specimens prepared by literature methods and were confirmed by analyses. Melting points were determined on a Kofler Microscope hot stage and are uncorrected. Infrared absorption spectra were recorded on Beckman Acculab-10 infrared spectrometer. The n.m.r. (300 MHz) and mass spectra were run at Department of Chemistry, University of Sherbrooke, Canada.

Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate(I). To hexamethylenetetramine (2.33 g; 0.0166 mole) dissolved in water (25 ml) was gradually added ethyl acetoacetate (6.50g; 0.05 mole) and shaken thoroughly

to dissolve. The volume of the reaction mixture was made up to 50 ml by addition of water. It was allowed to stand at room temperature (30±3°) with occasional shaking. After 5 days yellow fluffy compound (4.71 g; 74.5%) was obtained, which on recrystallization from ethanol afforded yellow crystals m.p. 181-183°, lit. (34, 35) m.p. 176-183°. Its mass spectrum indicated molecular ion at m/z 253 corresponding to its molecular formula, $C_{13}H_{19}NO_4$. Its i.r., and n.m.r. spectra superimposed on respective spectrum of the authentic sample.

3,5-Diacetyl-1,4-dihydro-2,6-dimethylpyridine(II). Acetylacetone (5.0 g; 0.05) mole) was slowly added to a solution of hexamethylenetetramine (0.875 g; 0.00625 mole) dissolved in water (25 ml) and shaken vigorously until homogeneous. The volume of the reaction mixture was then made up to 50 ml and shaken gently till a clear solution was obtained. The reaction mixture was kept at room temperature (30±3°) for 3 days to yield yellow short needles (2.56 g; 53.1%) which on recrystallization from ethanol yielded bright yellow fluffy needles melting at 198° with decomposition, lit. (39) m.p. 198°. Its molecular ion (m/z 193) agreed with its molecular formula, $C_{11}H_{15}NO_2$. Its i.r. and n.m.r. spectra were found to be identical to respective spectrum of an authentic sample.

Bis-(2,6-dioxo-4,4-dimethylcyclohexyl) methane(III). Dimedone (560 mg; 0.004 mole) and hexamethylenetetramine (140 mg; 0.001 mole) were dissolved in 12 ml of 1,4-dioxan-water mixture (2:1) and were heated to 72±3° for 5-7 minutes until white crystalline compound precipitated. The reaction mixture was cooled to below room temperature by immersing the reaction flask in cold water. White crystals (284 mg; 48.9%) obtained, upon recrystallization from ethanol-water gave white needles m.p. 190-192°, lit. (44) m.p. 191-192°. Its ^1H n.m.r. ($CDCl_3$) spectrum signalled absorptions at 1.03 (singlet, CH_3protons), 2.27 (singlet, CH_2protons), 3.14 (singlet, CH_2 protons and 11.60 ppm (broad singlet, OH protons) and the integration of these signals was in the ratio 6:4:1:1 respectively. Reaction in ethanol-water (1:1, 20 ml) afforded 280 mg (48.3%) of the compound.

1,8-Dioxo-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydro acridin (IV). Dimedone (560 mg; 0.004 mole) and hexamethylenetetramine (140 mg; 0.001 mole) were dissolved in 12 ml of 1,4-dioxan-water mixture (2:1). The mixture was refluxed gently for 1-2 hrs., diluted with water (5 ml) and allowed to stand at low temperature (13±2°). Pale yellow compound (242 mg; 44.3%) precipitated after one day was purified by recrystallization from ethanol to yield white needles m.p. 263-267° (decomp.), lit. (41) m.p. 267°. Its i.r. spectrum superimposed on the i.r. spectrum of a sample prepared by a reported method (41). Reaction in 20 ml of ethanol-water (1:1) in presence of conc. hydrochloric acid (0.1 ml) afforded 250 mg (45.8%) of the compound.

α,α, ,γ ,γ tetrabenzoylpropane (V). Dibenzoylmethane (448 mg; 0.002 mole), hexamethylenetetramine (140 mg; 0.001 mole) and concentrated hydrochloric acid (0.1 ml) were dissolved in 30 ml of ethanol-water mixture (2:1) and refluxed for 2 hr. At the end of the reaction, the mixture was diluted with water (5 ml) and allowed to stand at low temperature (13±2°) for a day. The compound precipitated (white crystals, 250 mg; 54.3%), was recrystallized from ethanol to afford white granules m.p. 175-177°, lit. (44,45) m.p. 176-177°. Its i.r. spectrum exactly matched with the spectrum of the sample prepared by literature method (45). Its ^1H n.m.r. ($CDCl_3$) signalled absorption at 2.80 (triplet, methylene protons), 5.79 (triplet, methine protons), 7.50 (triplet, aromatic *meta* protons), 7.58 (triplet, aromatic *para* protons) and 8.18 ppm (triplet, ortho protons) in the ratio of 1:1:4:2:4 as expected. however, its molecular ion signalled peak at m/z 442 (instead of 460) which corresponds to its dehydrated product.

Results and Discussion

The reaction of ethyl acetoacetate with hexamethylenetetramine at room temperature (30±3°) or below room temperature (13±3°) in varying molar ratio and molar concentrations at different pH's developed or adjusted by the addition of conc. hydrochloric acid and sodium hydroxide yielded diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (I) from 11.4 to 80.3%, after 5-21 days. The results are recorded in Table 1. Maximum yield of the pure compound (I) (4.72 g; 74.7%) at room temperature (30±3°) was obtained after 7 days when ethyl acetoacetate and hexamine were allowed to react in the molar ratio 1:1/4. The molar concentration of ethyl acetoacetate being 1 mole/litre and the pH of the reaction was 7.3. at lower temperatures (13±2°) the reaction proceeds at a very slow rate. When the reaction was carried out in solvents (acetone, methanol and ethanol) at room temperature and under reflux, a small amount of the compound (7.1%) could be obtained only in methanol after 8 hr of refluxing.

The reaction of acetylacetone and hexamine in the molar ratios 1:1/3, 1:1/4 and 1:1/8 in the aqueous medium at room temperature (30±3°) or below (13±2°) with molar concentrations (of acetylacetone) varying from 0.25 to 2 moles/litre yielded 3,5-diacetyl-1,4-dihydro-2,6-dimethylpyridine (II). The results are presented in Table 2. Acetylacetone and hexamine in the molar ratio 1:1/8 with molar concentration of acetylacetone at 1 mole/litre in the aqueous medium at 30±3° yield maximum of the product (53.1%) after 3 days. If acetylacetone and hexamine in the

Table 1 Diethyl 1,4-Dihydro-2,6-Dimethylpyridine-3,5-Dicarboxylate (I) from Ethyl Acetoacetate and Hexamine in Water

Sr. No.	Ethyl acetoacetate (moles/molar conc.)	Hexamine (moles)	Molar ratio (Ester: amine)	Volume ml	pH	Tempe-rature °C	Duration days	Yield (%)
1.	0.05/1	0.10	1:2	50	7.79	30±3	05	81.3 crude
2.	"	0.05	1:1	"	7.72	"	05	77.7 "
3.	"	0.0333	1:2/3	"	7.70	"	05	76.3 "
4.	"	0.025	1:1/4	"	7.45	"	05	71.3 "
5.	"	0.016	1:1/3	"	7.33	"	05	74.5 pure
6.	"	0.0125	1:1/4	"	7.30	"	06	69.7 "
	"	"	"	"	"	"	07	74.7 "
7.	"	0.00625	1:1/8	"	7.05	"	06	23.4 "
		"	"	"	"	"	07	24.9 "
8.		0.0166	1:1/3	"	7.46	13±2	21	38.2 "
9.	0.05/2	"	"	25	7.45	30±3	05	50.5 crude
10.	"	"	"	"	7.56	13±2	21	25.8 "
11.	0.05/0.5	"	"	100	7.25	30±3	05	64.8 pure
12.	"	"	"	"	7.36	13±2	21	34.0 "
13.	0.05/0.25	"	"	200	7.13	30±3	05	33.2 "
14.	0.05/0.25	0.0166	1:1/3	200	7.24	13±2	1	34.0 pure
15.	0.05/1	"	"	50	6.02	30±3	06	49.0 crude
16.	"	"	"	"	4.86	"	06	11.4 "
17.	"	"	"	"	0.82	"	06	Nil
18.	"	"	"	"	8.64	"	06	73.2 "
19.	"	"	"	"	9.84	"	06	62.5 "
20.	"	"	"	"	13.03	"	06	Nil
21.	"	"	"	50 acetone	–	"	06	Nil
	"	"	"		–	reflux	8 hrs.	Nil
22.				50		30±3	06	Nil
	"	"	"	Methanol	–			
						reflux	8 hrs.	7.1 pure
23.				50		30±3	06	Nil
				Ethanol		reflux	8 hrs.	

Table 2. 3,5-Diacetyl-1,4-Dihydro-2,6-Dimethylpyridine (II) from Acetylacetone and Hexamine in Water

Sr. No.	Acetylacetone (moles/molar conc.)	Hexamine (moles)	Molar ratio	Water ml	pH	Tempe-rature	Duration days	Yield (%)
1.	0.05/2	0.0166	1:1/3	25	7.11	30±3	02	49.3 crude
2.	0.05/1	"	"	50	7.12	"	02	43.5 pure
3.	"	"	"	50	7.15	13±2	50	59.27 "
4.	0.05/0.5	"	"	100	7.14	30±3	02	38.5 "
5.	0.5/0.25	"	"	200	7.17	"	03	34.8 "
6.	0.05/1	0.0125	1:1/4	50	6.84	"	03	47.9 "
7.	"	0.00625	1:1/8	50	6.75	"	03	53.1 "
8.	0.05/2	"	"	25	6.71	"	03	54.1 crude
9.	0.05/0.5	"	"	100	6.79	"	04	44.1 pure
	0.05/0.25	"	"	200	6.89	"	05	40.4 "

TABLE 3. REACTIONS OF DIMEDONE AND DIBENZOYLMETHANE WITH HEXAMINE UNDER DIFFERENT PARAMETERS.

Sr. No.	β-Diketone (moles)	Hexamine (moles)	Molar ratio	Solvent System	Catalyst HCl (Conc.)	Conditions	Product Yield (%)
	Dimedone						
1.	0.004	0.001	1:1/4	1,4-Dioxan -water 1:2 (12 ml)	Nil	30±3° (1 day)	(III) 45.5
2.	"	"	"	"	Nil	72±3° (5-7 min.)	(III) 48.9
3.	"	"	"	"	Nil	reflux (1-2 hr.)	(IV) 44.3
4.	"	"	"	Ethanol:water 1:1 (20 ml)	Nil	30±3°(1 day)	(III)33.3
5.	"	"	"	"	Nil	73±3°(5-7 min.)	(III) 48.3
6.	"	"	"	"	0.1 ml	"	(III) 49.1
7.	"	"	"	"	Nil	Reflux(1-2 hrs.)	(IV) 20.1
8.	"	"	"	"	0.1 ml	"	(IV) 45.8
9.	"	"	"	2:1 (20 ml)	Nil	30±3°(1 day)	(III) 32.1
10.	"	"	"	"	Nil	72±3°(5-7 min.)	(III) 47.4
11.	0.004	0.001	1:1/4	2:1 (20 ml)	0.1 ml	72±3°(5-7 min.)	(III) 48.8
12.	"	"	"	"	Nil	reflux(1-2 hr.)	(IV) 25.6
13.	"	"	"	"	0.1 ml	hr.	(IV) 57.8 crude
14.	Dibenzoyl-methane (moles)			Ethanol-water			
	0.002	0.001	1:1/2	2:1	0.1 ml	30±3°(1 day)	
	"	"	"	30 ml)			
15.	"	"	"	"	"	72±3°(5-7 min.)	(V) 50.01
16.	"	"	"	"	"	reflux(1-2 hr.)	(V) 54.3

molar ratio 1:1/3 are allowed to react at lower temperatures (13±2°) an improved yield (59.27%) is obtained but only after an extended period of 50 days.

Dimedone and hexamine in the molar ratio 1:1/4 dissolved in 1,4-dioxan-water mixture when allowed to stand at room temperature (30±3°) for one day yielded methylene-*bis*-dimedone (III) in 45.5% yield Table 3. At 72±3° after only 5-7 minutes the yield increased to 48.9%. However, when the reaction mixture was refluxed for 1-2 hr it afforded 44.3% of the dihydropyridine derivative (IV). The maximum yield of (III) (49.1%) was obtained when 0.004 molar of dimedone, 0.001 moles of hexamine (in the molar ratio 1:1/4) and 0.1 ml of concentrated hydrochloric acid in 20 ml of ethanol:water (1:1) were heated to 72±3° for 5-7 min. Mild refluxing for 1-2 hr. afforded dihydropyridine derivative (IV) in 45.8% yield.

Dibenzoylmethane (0.002 moles) and hexamine (0.001 moles) in the molar ratio 1:1/2 in ethanol-water (2:1) mixture (30 ml) in the presence of con. hydrochloric acid (0.1 ml) gave methylene-*bis*-(dibenzoylmethane). (V) in 50% yield when heated at 72±3° for 5-7 min. Only the yield could be improved (54.3%) by refluxing the reaction mixture for 1-2 hr and under no conditions the dihydropyridine derivative of dibenzoylmethane could be obtained. The results are shown in Table 3.

TABLE 4. POSITIONS OF EQUILIBRIA (48-51) OF DIFFERENT B-DIKETONES/B-KETO ESTERS AFFECTING DIHYDROPYRIDINES FORMATION

	% enol (liquid.)	%enol (hexane)	%enol (aqueous) solutio	%dihydro-pyridine
Ethyl acetoacetate	7.8	48	0.4	74.5
Acetylacetone	76.4	92	15.5	53.1
Dimedone			95.3	44.3
Dibenzoylmethane			100 (alcohol)	

The results of these investigations show that our methods of synthesising dihydropyridine derivatives by using hexamine with ethyl acetoacetate, acetylacetone and dimedone are single-step, simple, convenient and economical as compared to literature methods.

It appears that ethyl acetoacetate, and acetylacetone both yield corresponding dihydropyridine derivatives in the aqueous medium proportional to the extent of the keto form of these compounds as may be seen from Table 4. However, this version is not applicable in case of dimedone, which also yields its dihydropyridine derivative,while dibenzoylmethane is restricted to its *bis*-compound.

In order to explain this deviation we have to turn to an other factor which serves to stabilize the enol with respect to the keto form. That is the possibility of strong intramolecular hydrogen bonding in case of ethyl acetoacetate, acetylacetone and dibenzoylmethane as show in VI, VII and VIII conformations. Such a 'folded up' conformation is geomotrically impossible in dimedone. However, it may undergo enol-chelate dimerisation (IX) and thus stabilizes itself, which may be even more pronounced in methylene-*bis*-dimedone conformation (X). Consequently, the *bis*-dimedone is obtained under mild conditions. The enolic form of this *bis*-compound is quite evident from its n.m.r. spectrum, which shows broad absorption centre at 11.60 ppm for two enolic hydroxy groups of this compound. On refluxing it is likely to overcome this stabilization and if not isolated may form dihydropyridine derivative, which is actually the case.

No doubt dibenzoylmethane exists almost exclusively in the enol form and has strong intramolecular hydrogen bonding in the "folded" compact formation. However, the n.m.r. spectrum of its *bis*-compound shows triplet for methylene and methine protons at 2.80 and 5.79 ppm., respectively, which suggests that it should be predominantly in the ketonic form. Consequently, a strain free conformation (XI), which is energetically more favourable than any other possible conformation, may be proposed for this *bis*-compound. This proposal is in conformity with an other derivative of dibenzoylmethane for which *anti*-configuration has also been put forward [52]. Different structures and conformations have been shown in Chart 1 and 2.

An other point worth consideration is that the reaction of

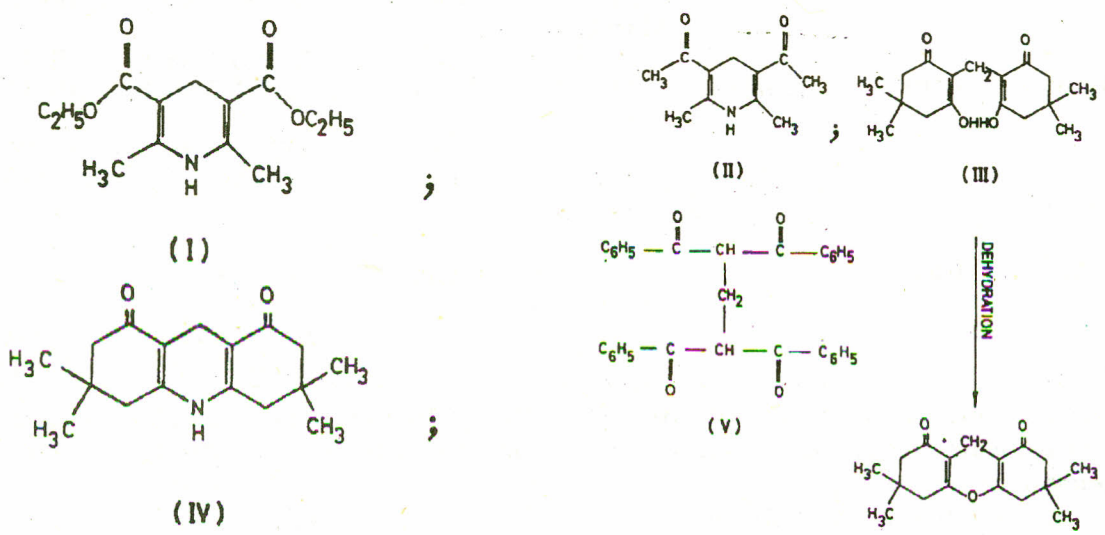

Chart I. Products obtained from Reactions of β-Keto Ester/β-Diketones

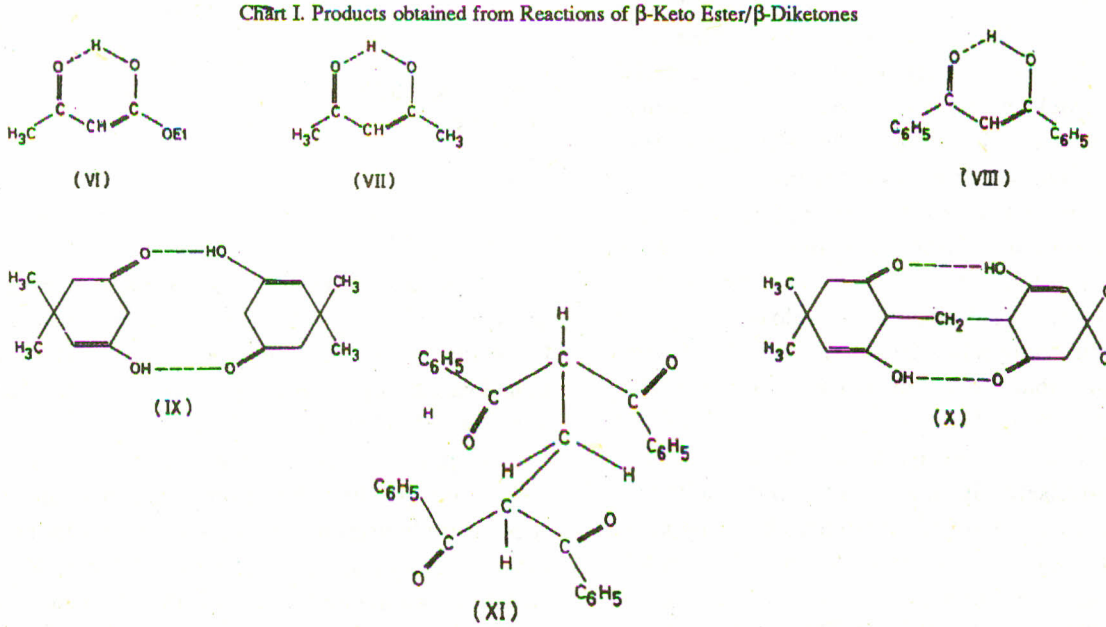

Chart II. Inter and intramolecular stabilisation in β-Keto ester and β-Diketones and their derivatives.

hexamine with β-diketones/β-keto ester yielding dihydropyridine derivatives is taking place at around neutral pH and neither formaldehyde nor ammonia was detected in the reaction mixture. Hence, it may be inferred that this reaction is taking place without involving free formaldehyde and ammonia, which are normally produced only under acidic conditions. Hence, this observation suggests that both ethyl acetoacetate and acetylacetone react with hexamine concomitantly. Such a concerted reaction may not be necessarily operative, when dimedone is used, since its *bis*-compound was also insoluble, and which *in situ* eventually transforms to the dihydropyridine stage probably through its dehydrated derivative [42].

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